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(21) International Application Number: PCT/SE95/01542 (22) International Filing Date: 19 December 1995 (19.12.95) (30) Priority Data: 9404469-0 22 December 1994 (22.12.94) SE 9502452-7 6 July 1995 (06.07.95) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (73) Inventors/Applicants (for US only): BÄCKSTRÖM, Kjell [SE/SE]; Notariegränden 4, S-226 47 Lund (SE). DAHLBÄCK, Magnus [SE/SE]; Sköldgränden 10, S-224 75 Lund (SE). JOHANSSON, Ann [SE/SE]; Arkeologvägen 65, S-226 54 Lund (SE). KÄLLSTRAND, Göran [SE/SE]; Dragonvägen 1, S-237 32 Bjärred (SE). LINDQVIST, Elisabet [SE/SE]; Lärkvägen 4, S-227 31 Lund (SE). (74) Agents: PÅRUP, Mats et al.; Astra Aktiebolag, Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG). Published <i>With international search report.</i>
(54) Title: AEROSOL DRUG FORMULATIONS (57) Abstract Aerosol formulations suitable for use in pressurised metered dose inhalers comprise a hydrofluoroalkane propellant, a medicament for inhalation and a surfactant which is a C ₈ -C ₁₆ fatty acid or salt thereof, a bile salt, a phospholipid, or an alkyl saccharide.		

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AEROSOL DRUG FORMULATIONS

Field of the Invention

The present invention relates to aerosol formulations suitable for use in pressurised metered dose inhalers (pMDI's). More particularly, it relates to a formulation including a hydrofluoroalkane (HFA) propellant and a particularly suitable surface active-dispersing agent.

Background of the invention

Medicaments for treating respiratory and nasal disorders are frequently administered in aerosol formulations through the mouth or nose. One widely used method for dispensing such an aerosol formulation involves making a suspension formulation of the medicament as a finely divided powder in a liquefied gas known as a propellant. Pressurised metered dose inhalers, or (pMDI's) are normally used to dispense such formulations to a patient. Surface active agents, or surfactants, are commonly included in order to aid dispersion of the medicament in the propellant and to prevent aggregation of the micronised medicament particles, and to improve lubrication of the valve.

Until recently, chlorofluorocarbon-containing propellants (CFC's) were accepted for use in all pharmaceutical aerosol formulations. Typical surfactant dispersing agents used in the CFC formulations were for example sorbitantriolate, oleic acid, lecithines, and ethanol. Since CFC's have been implicated in the destruction of the ozone layer, a new generation of propellants has emerged to take their place.

Hydrofluoroalkane (HFA) propellants for example 1,1,1,2-tetrafluoroethane (P134a), 1,1,1,2,3,3,3-heptafluoropropane (P227) and 1,1-difluoroethane (P152a) are today considered to be the most promising new propellants. Not only are they environmentally acceptable, but they also have low toxicity and vapour pressures suitable for use in aerosols. However, the surfactants commonly used with the CFC formulations are not necessarily suitable for use with the new generation of propellants. Various alternative surfactants have been proposed.

For example, WO 92/00061 discloses polyethoxylated surfactant for use with hydrofluorocarbon propellants. WO 91/11173 discloses fluorinated surfactants. WO 91/14422 discloses perfluorinated carboxylic acid propellants for use with hydrofluorocarbon propellants. WO 92/00107 discloses the use of a 1,1,1,2-tetrafluoroethane -soluble surfactant with 1,1,1,2- tetrafluoroethane propellant.

Summary of the invention

It has now been found that certain specific classes of surfactant are particularly suitable for use with the new generation of propellant.

Accordingly, the present invention provides a pharmaceutical aerosol formulation comprising a hydrofluoroalkane propellant or a mixture of hydrofluoroalkane propellants, a physiologically effective amount of a medicament for inhalation and a surfactant selected from a C₈-C₁₆ fatty acid or salt thereof, a bile salt, a phospholipid or an alkyl saccharide.

The surfactants employed in the present invention give fine dispersions in the new propellants, with good stability. The inventive formulations are therefore useful for administering inhalable medicaments.

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Of the fatty acid surfactants and salts thereof, C₈-C₁₆ fatty acids salts are preferred. Examples of preferred fatty acid salts are sodium, potassium and lysine salts of caprylate (C₈), caprate (C₁₀), laurate (C₁₂) and myristate (C₁₄). As the nature of the counterion is not of special significance, any of the salts of the fatty acids are potentially useful. A particularly preferred fatty acid salt is sodium caprate.

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Suitable bile salts may be for example salts of cholic acid, chenodeoxycholic acid, glycocholic acid, taurocholic acid, glycochenodeoxycholic acid, taurochenodeoxycholic acid, deoxycholic acid, glycodeoxycholic acid, taurodeoxycholic acid, lithocholic acid, and ursodeoxycholic acid.

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Of the bile salts, trihydroxy bile salts are preferred. More preferred are the salts of cholic, glycocholic and taurocholic acids, especially the sodium and potassium salts thereof. The most preferred bile salt is sodium taurocholate.

- 5 Suitable phospholipids may be for example single-chain phospholipids, for example lysophosphatidylcholines, lysophosphatidylglycerols, lysophosphatidylethanolamines, lysophosphatidylinositols and lysophosphatidylserines or double-chain phospholipids, for example diacylphosphatidylcholines, diacylphosphatidylglycerols, diacylphosphatidylethanolamines, diacylphosphatidylinositols and
10 diacylphosphatidylserines.

Of the phospholipids, diacylphosphatidylglycerols and diacylphosphatidylcholines are preferred, for example dioctanoylphosphatidylglycerol and dioctanoylphosphatidylcholine.

- 15 Suitable alkyl saccharides may be for example alkyl glucosides or alkyl maltosides, for example decyl glucoside and dodecyl maltoside.

The most preferred surfactants are bile salts.

- 20 The propellant may comprise for example one or more of 1,1,1,2-tetrafluoroethane (P134a), 1,1,1,2,3,3,3-heptafluoropropane (P227) and 1,1-difluoroethane (P152a), optionally in admixture with one or more other propellants. Preferably the propellant comprises 1,1,1,2-tetrafluoroethane (P134a) or 1,1,1,2,3,3,3-heptafluoropropane (P227), or a mixture of P134a and P227, for example a density-matched mixture of P134a and P227.

- 25 In addition to medicament, propellant and surfactant, a small amount of ethanol (normally up to 5% but possibly up to 20%, by weight) may be included in the formulations of the present invention. Ethanol is commonly included in aerosol compositions as it can improve the function of the metering valve and in some cases also improve the stability of
30 the dispersion.

Medicaments suitable for inclusion in the formulation of the present invention are any which may be delivered by inhalation. Suitable inhalable medicaments may include for example β 2-adrenoreceptor agonists for example salbutamol, terbutaline, rimeterol, fenoterol, reproterol, adrenaline, pirbuterol, isoprenaline, orciprenaline, bitolterol, salmeterol, formoterol, clenbuterol, procaterol, broxaterol, picumeterol, TA-2005, mabuterol and the like, and their pharmacologically acceptable esters and salts; anticholinergic bronchodilators for example ipratropium bromide and the like; glucocorticosteroids for example beclomethasone, fluticasone, budesonide, tipredane, dexamethasone, betamethasone, fluocinolone, triamcinolone acetonide, mometasone, and the like, and their pharmacologically acceptable esters and salts; anti-allergic medicaments for example sodium cromoglycate and nedocromil sodium; expectorants; mucolytics; antihistamines; cyclooxygenase inhibitors; leukotriene synthesis inhibitors; leukotriene antagonists, phospholipase-A2 (PLA2) inhibitors, platelet aggregating factor (PAF) antagonists and prophylactics of asthma; antiarrhythmic medicaments, tranquilisers, cardiac glycosides, hormones, anti-hypertensive medicaments, antidiabetic- antiparasitic- and anticancer- medicaments, sedatives and analgesic medicaments, antibiotics, antirheumatic medicaments, immunotherapies, antifungal and antihypotension medicaments, vaccines, antiviral medicaments, proteins, peptides, vitamins and others, for example cell surface receptor blockers, antioxidants, free radical scavengers and organic salts of N,N'-diacetylcystine.

Combinations of medicaments are also suitable, for example a combination of formoterol and budesonide.

The medicaments may be used in the form of salts or esters or solvates (hydrates), where appropriate.

Other ingredients may be added into the formulation of the present invention, if desired. Such ingredients may be for example other pharmaceutically active agents, adjuvants, carriers, flavouring agents, buffers, antioxidants, chemical stabilisers and the like.

Preferably the surfactant and medicament are present in the present invention in a ratio of approximately 1 : 50 to 1 : 0.2. The preferred concentration of medicament in the formulations of the present invention is 0.1 mg/ml to 25 mg/ml.

5 "A medicament for inhalation" means a medicament which is suitable for inhalation and which consists largely of particles in a size range appropriate for maximal deposition in the lower respiratory tract (i.e., under 10 microns). Therefore as much as possible of the medicament preferably consists of particles having a diameter of less than 10 microns, for example 0.01-10 microns or 0.1-6 microns, for example 0.1-5 microns. Preferably at least
10 50% of the medicament consists of particles within the desired size range. For example at least 60%, preferably at least 70%, more preferably at least 80% and most preferably at least 90% of the medicament consists of particles within the desired size range.

Therefore, the medicament for use in the present invention may have to be processed prior
15 to inclusion in the formulations, in order to produce particles in the desired size range. For example the medicament may be micronised, for example out in a suitable mill, for example a jet mill. Alternatively, particles in the desired particle range may be obtained by for example spray drying or controlled crystallisation methods, for example crystallisation using supercritical fluids.

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Preferably, the surfactant for use in the present invention is also in the desired particle size range.

Where the surfactant and medicament are both micronised, they may be dry mixed and then
25 micronised together, or they may be micronised separately and then mixed. The propellant and optional ethanol may be added thereafter.

Alternatively a portion of the micronised surfactant may be cold-mixed with a portion of the propellant and optional ethanol, whereafter the micronised medicament may be added.
30 After mixing in of the medicament the remaining surfactant and propellant and optional ethanol may be added and the suspension filled into appropriate containers.

The aerosol formulation of the present invention is useful for the local or systemic treatment of diseases and may be administered for example via the upper and lower respiratory tract, including by the nasal route. As such the present invention also provides
5 said aerosol formulation for use in therapy; the use of the aerosol formulation in the manufacture of a medicament for the treatment of diseases via the respiratory tract; and a method for the treatment of a patient in need of therapy, comprising administering to said patient a therapeutically effective amount of the aerosol formulation of the present invention.

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The following Examples are intended to illustrate, but not limit, the invention:

Formulations of various medicaments in P134a and/or P227 with different surfactants were prepared in order to assess the quality of the suspensions formed. In the following
15 examples the quality of the suspension is rated as "acceptable" or "good". An acceptable suspension is characterised by one or more of slow settling or separation, ready re-dispersion, little flocculation, and absence of crystallisation or morphology changes, such that the dispersion is sufficiently stable to give a uniform dosing. A good dispersion is even more stable.

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Example 1

Micronised formoterol fumarate (1 part) and micronised sodium taurocholate (2 parts) (total 5 mg) were added to a plastic coated glass bottle. The bottle was chilled to approximately -40°C with a mixture of carbon dioxide ice and isopropanol, and 10 ml
25 chilled P134a (at approximately -40°C) was added. The bottle was sealed with a metering valve and treated in an ultrasonic bath for about 10 minutes.

A good suspension formed.

Example 2

Micronised budesonide (10 parts) and micronised sodium taurocholate (2 parts) (total 5 mg) were added to a plastic coated glass bottle. The bottle was chilled to approximately -40°C with a mixture of carbon dioxide ice and isopropanol, and 10 ml chilled P134a (at approximately -40°C) was added. The bottle was sealed with a metering valve and treated in an ultrasonic bath for about 10 minutes.

A good suspension formed.

Example 3

Micronised salbutamol sulphate (10 parts) and micronised sodium taurocholate (2 parts) (total 5 mg) were added to a plastic coated glass bottle. The bottle was chilled to approximately -40°C with a mixture of carbon dioxide ice and isopropanol, and 10 ml chilled P134a (at approximately -40°C) was added. The bottle was sealed with a metering valve and treated in an ultrasonic bath for about 10 minutes.

A good suspension formed.

Example 4

Micronised ipratropium bromide (1 part) and micronised sodium taurocholate (2 parts) (total 5 mg) were added to a plastic coated glass bottle. The bottle was chilled to approximately -40°C with a mixture of carbon dioxide ice and isopropanol, and 10 ml chilled P134a (at approximately -40°C) was added. The bottle was sealed with a metering valve and treated in an ultrasonic bath for about 10 minutes.

A good suspension formed.

Examples 5-8

Examples 1-4 were repeated, substituting propellant P227 for P134a. In all cases, good suspensions formed.

Examples 9-16

Examples 1-8 were repeated with the following addition: ethanol, approximately 650 μ l, was added to the chilled bottle before sealing with the metering valve. In all cases, acceptable suspensions formed.

Claims

1. A pharmaceutical aerosol formulation comprising a HFA propellant; a physiologically effective amount of a medicament for inhalation; and a surfactant which is
5 a C₈-C₁₆ fatty acid or salt thereof, a bile salt, a phospholipid, or an alkyl saccharide.
2. A pharmaceutical aerosol formulation as claimed in claim 1, wherein the surfactant is a C₈-C₁₆ fatty acid salt.
- 10 3. A pharmaceutical aerosol formulation as claimed in claim 2, wherein the fatty acid salt is selected from the sodium, potassium and lysine salts of caprylate (C₈), caprate (C₁₀), laurate (C₁₂) and myristate (C₁₄).
4. A pharmaceutical aerosol formulation as claimed in claim 1, wherein the surfactant is
15 a trihydroxy bile salt.
5. A pharmaceutical aerosol formulation as claimed in claim 4, wherein the bile salt is selected from the salts of cholic, glycocholic and taurocholic acids.
- 20 6. A pharmaceutical aerosol formulation as claimed in claim 5, wherein the bile salt is selected from the sodium and potassium salts of cholic, glycocholic and taurocholic acids.
7. A pharmaceutical aerosol formulation as claimed in claim 6, wherein the bile salt is -
sodium taurocholate.
- 25 8. A pharmaceutical aerosol formulation as claimed in claim 1, wherein the surfactant is a single-chain phospholipid.

9. A pharmaceutical aerosol formulation as claimed in claim 8, wherein the surfactant is selected from lysophosphatidylcholines, lysophosphatidylglycerols, lysophosphatidylethanolamines, lysophosphatidylinositols and lysophosphatidylserines.

5 10. A pharmaceutical aerosol formulation as claimed in claim 1, wherein the surfactant is a double-chain phospholipid.

11. A pharmaceutical aerosol formulation as claimed in claim 10, wherein the surfactant is selected from diacylphosphatidylcholines, diacylphosphatidylglycerols,
10 diacylphosphatidylethanolamines, diacylphosphatidylinositols and diacylphosphatidylserines.

12. A pharmaceutical aerosol formulation as claimed in claim 11, wherein the surfactant is selected from dioctanoylphosphatidylglycerol and dioctanoylphosphatidylcholine.

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13. A pharmaceutical aerosol formulation as claimed in claim 1, wherein the surfactant is selected from alkyl glucosides and alkyl maltosides.

14. A pharmaceutical aerosol formulation as claimed in claim 13, wherein the surfactant is
20 selected from decyl glucoside and dodecyl maltoside.

15. A pharmaceutical aerosol formulation as claimed in any of claims 1-14, wherein the propellant comprises 1,1,1,2-tetrafluoroethane (P134a), 1,1,1,2,3,3,3-heptafluoropropane (P227) or 1,1-difluoroethane (P152a).

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16. A pharmaceutical aerosol formulation as claimed in claim 15, wherein the propellant comprises 1,1,1,2-tetrafluoroethane (P134a) and 1,1,1,2,3,3,3-heptafluoropropane (P227).

17. A pharmaceutical aerosol formulation as claimed in claim 15 or 16, wherein the
30 propellant comprises a density-matched mixture of 1,1,1,2-tetrafluoroethane (P134a) and 1,1,1,2,3,3,3-heptafluoropropane (P227).

18. A pharmaceutical aerosol formulation as claimed in any preceding claim, wherein the medicament is a β 2-adrenoreceptor agonist, an anticholinergic bronchodilator, or a glucocorticosteroid.

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19. A pharmaceutical aerosol formulation as claimed in claim 18, wherein the medicament is selected from salbutamol, terbutaline, rimeterol, fenoterol, reproterol, adrenaline, pirbuterol, isoprenaline, orciprenaline, bitolterol, salmeterol, formoterol, clenbuterol, procaterol, broxaterol, picumeterol, TA-2005, mabuterol, ipratropium bromide,
10 beclomethasone, fluticasone, budesonide, tiopredane, dexamethasone, betamethasone, fluocinolone, triamcinolone acetonide, mometasone, and pharmacologically acceptable esters and salts thereof.

20. A pharmaceutical aerosol formulation as claimed in any of claims 1-17, wherein the
15 medicament is select from anti-allergic medicaments; expectorants; mucolytics; antihistamines; cyclooxygenase inhibitors; leukotriene synthesis inhibitors; leukotriene antagonists, phospholipase-A2 (PLA2) inhibitors, platelet aggregating factor (PAF) antagonists and prophylactics of asthma; antiarrhythmic medicaments, tranquilisers, cardiac glycosides, hormones, anti-hypertensive medicaments, antidiabetic- antiparasitic-
20 and anticancer- medicaments, sedatives and analgesic medicaments, antibiotics, antirheumatic medicaments, immunotherapies, antifungal and antihypotension medicaments, vaccines, antiviral medicaments, proteins, peptides, vitamins, cell surface receptor blockers, antioxidants, free radical scavengers and organic salts of N,N'-diacetylcystine.

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21. A pharmaceutical aerosol formulation as claimed in any preceding claim, including ethanol in an amount of up to 20% by weight of propellant and surfactant.

22. A pharmaceutical aerosol formulation as claimed in any preceding claim, including
30 ethanol in an amount of up to 5% by weight of propellant and surfactant.

23. A pharmaceutical aerosol formulation as claimed in any preceding claim, including other pharmaceutically active agents selected from adjuvants, carriers, flavouring agents, buffers, antioxidants and chemical stabilisers.

5 24. A pharmaceutical aerosol formulation as claimed in any preceding claim, wherein the surfactant is present in a surfactant : medicament ratio in the range of 1:50 to 1:0.2.

25. A pharmaceutical aerosol formulation as claimed in any preceding claim, wherein the medicament comprises particles having a diameter of 0.01-10 microns.

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26. A pharmaceutical aerosol formulation as claimed in claim 34, wherein the medicament comprises particles having a diameter of 0.1-6 microns.

27. A pharmaceutical aerosol formulation as claimed in claim 34, wherein the medicament
15 comprises particles having a diameter of 0.1-5 microns.

28. A pharmaceutical aerosol formulation as claimed in any of claims 25-27, wherein at least 50% of the medicament consists of particles within the said size range.

20 29. A pharmaceutical aerosol formulation as claimed in any of claims 25-27, wherein at least 60% of the medicament consists of particles within the said size range.

30. A pharmaceutical aerosol formulation as claimed in any of claims 25-27, wherein at least 70% of the medicament consists of particles within the said size range.

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31. A pharmaceutical aerosol formulation as claimed in any of claims 25-27, wherein at least 80% of the medicament consists of particles within the said size range.

32. A pharmaceutical aerosol formulation as claimed in any of claims 25-27, wherein at
30 least 90% of the medicament consists of particles within the said size range.

33. A pharmaceutical aerosol formulation as claimed in any preceding claim, wherein the concentration of medicament is 0.1 mg/ml to 25 mg/ml of the formulation.
34. A method for the manufacture of a pharmaceutical aerosol formulation as claimed in
5 any of claims 1-33, comprising the steps of: mixing the medicament and the surfactant and to a vessel at low temperature; adding propellant and optional ethanol; mixing; and adding further propellant and optional ethanol.
35. A pharmaceutical aerosol formulation as claimed in any of claims 1-33, for use in
10 therapy.
36. The use of a pharmaceutical aerosol formulation as claimed in any of claims 1-33 in the manufacture of a medicament for the treatment of diseases via the respiratory tract.
37. A method for the treatment of a patient in need of therapy, comprising administering to
15 said patient a therapeutically effective amount of the pharmaceutical aerosol formulation as claimed in any of claims 1-33.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 95/01542

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/12, A61K 47/12, A61K 47/24, A61K 47/26, A61K 47/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPIL, CLAIMS, EMBASE, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0518600 A1 (SCHERING CORPORATION), 16 December 1992 (16.12.92), page 3, line 24 - line 58, Example X	1-36
	--	
A	WO 9111495 A1 (BOEHRINGER INGELHEIM INTERNATIONAL GMBH ET AL), 8 August 1991 (08.08.91)	1-36
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☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

27 March 1996

02 -04- 1996

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 95/01542

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 37
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

05/02/96

International application No.
PCT/SE 95/01542

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0518600	16/12/92	AU-A- 2017592	12/01/93
		CA-A- 2111002	23/12/92
		CN-A- 1067578	06/01/93
		CZ-A- 9302714	13/07/94
		EP-A- 0588897	30/03/94
		EP-A- 0656206	07/06/95
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